Remarks

Prior to entry of this amendment, claims 63-88 and 108-115 are pending in the application (though the Office action erroneously stated 63-88 and 108-114). Of the pending, claims 79-88 (Group IV) and 108-115 (Groups VI and VII) are withdrawn from consideration as drawn to non-elected Groups. Thus, claims 63-78 are currently under examination (of which claims 63-70 are considered linking claims and claims 71-78 are Group III).

By this amendment, claims 63, 64, 66, 69, 71, 72, 74 and 78 are amended (as discussed below). Claims 65 and 108-115 are cancelled without prejudice to their subject matter being pursued in later related filing(s). New claims 116-134 are added; it is believed these claims are encompassed in the elected Group.

After entry of this amendment, claims 63, 64, 66-88 and 116-134 are pending in the application, of which 63, 64, 66-78 and 116-134 are under examination. No new matter has been added by any of these amendments. Consideration, rejoinder (where appropriate) and allowance of the claims is respectfully requested.

Examiner Interview

Applicants thank Examiner Howard for taking the time for a telephone interview with their undersigned representative, Tanya Harding, on July 22, 2008. The Examiner was provided a draft of certain proposed claim amendments prior to the interview. During the interview, possible additional amendments to address the claim objections were discussed. Also discussed were the pending enablement rejections and possible rejoinder of species. Though full agreement was not reached on each topic discussed, it is believed that this response incorporates helpful suggestions from the Examiner.

Comments regarding the Claim Restrictions

Applicants acknowledge that Group III (claims 71-78) has been elected, and thank the Examiner for confirming that linking claims 63-70 (which link Groups III and IV) are under consideration. Applicants also thank the Examiner for indicating that claims 84-87 are now considered to be part of Group IV (along with claims 79-83 and 88). Applicants understand that

the claims of Group IV will be recombined and examined in the current case upon the allowance of any of the bridging claims (claims 63-70).

With regard to claims 108-115, which were added in prior filings, Applicants acknowledge that the Examiner has assigned these claims to new Group VII (transgenic animals and cells derived from said transgenic animals). Applicants also acknowledge that these claims have been withdrawn by the Examiner; Applicants have cancelled claims 108-115 by this amendment, without prejudice.

It is believed that the indication at line 7 of page 3 of the pending Office action is a clerical error, in that "Claims 108-116 (Group IV) ..." should read "Claims 108-115 (Group VII)..." and Applicants have proceeded based on this understanding.

Comments regarding the Species Elections

Applicants acknowledge that the requirement for election of a single species (species variant PDGFRA D842V (SEQ ID NOs: 3 and 4)) has been made final. Applicants understand that additional species will be examined when a claim that is generic for the species (that is, not specifically limited to the initially elected species) is found to be allowable. Applicants have therefore left the remaining species in the pending claims. Rejoinder of the non-elected species is earnestly sought.

Claim Objections

Various claims are objected to for specific informalities. Each alleged informality is addressed separately below.

Claim 63 is objected to for the erroneous reference to positions "2090 through 2937" in PDGFRA. Applicants thank the Examiner for identifying this clerical error, which has been corrected herein to read "2916 through 2937". Claim 63 is further objected for use of the acronym "PDGFRA". Though this is an art-recognized acronym, Applicants have done as suggested and spelled out the term the first time it is used in the claims.

Claims 64, 74, and 78 are objected to for alleged inconsistencies between the recited "variants" and the submitted Sequence List. Specifically, the following specific discrepancies are alleged (minor clerical errors in the following text have been corrected and are shown italicized, as discussed during the telephone interview):

(a) There is no "variant nucleic acid sequence" at position 2917 in SEQ ID NO: 5. Instead, SEQ ID NO: 5 has an 'a' residue at position 2917, as in the wild type sequence of SEQ ID NO: 1. This is confirmed by the alignment shown in Table 1.
(b) There is no "variant nucleic acid sequence" at position 2927 in SEQ ID NO: 7. Instead, SEQ ID NO: 7 has a 'c' residue at position 2927, as in the wild type sequence of SEQ ID NO: 1.
(c) There is no "variant nucleic acid sequence" at position *2075* in SEQ ID NO: 9. Instead, SEQ ID NO: 9 has a 'g' residue at position *2075*, as in the wild type sequence of SEQ ID NO: 1.
(d) There is no "variant nucleic acid sequence" at position 2089 in SEQ ID NO: 11. Instead, SEQ ID NO: 11 has a 'c' residue at position *2089*, as in the wild type sequence of SEQ ID NO: 1.
(e) There is no "variant nucleic acid sequence" at position 2017 in SEQ ID NO: 22. Instead, SEQ ID NO: 22 has an 'a' residue at position 2017, as in the wild type sequence of SEQ ID NO: 1.

As discussed during the interview, the terminology confusion appears to have arisen when references to amino acid variants (many of which were deletions or insertions) were converted to nucleic acid terminology. Applicants thank the Examiner for his willingness to entertain descriptions based on the amino acid sequence changes. As discussed in the telephone interview, Applicants have amended claims 64, 74, and 78 to refer to each "variant" with reference to the amino acid change (substitution, deletion, insertion, or combination thereof) rather than the nucleic acid position. This amendment is supported, for instance, in Tables 1 and 3 of the specification (reproduced below for convenience). It is believed this amendment fully obviates the objections to claims 64, 74, and 78 and Applicants request withdrawal of this objection.

Table 1 & 3 (from specification)

Genotype	DNA sequence (top line) Translation (bottom line)
PDGFRA Wild type (Ac. No. XM_011186; SEQ ID NOs: 1 and 2)	2906* GGCCTGGCCAGAGACATCATGCATGATTCGAACTATGTG 838 G L A R D I M H D S N Y V
D842V (SEQ ID NOs: 3 and 4)	2906 GGCCTGGCCAGAG**T**CATCATGCATGATTCGAACTATGTG 838 G L A R **V** I M H D S N Y V
Deletion of DIMH842-845 (SEQ ID NOs: 5 and 6)	2906 GGCCTGGCCAGA----------GATTCGAACTATGTG 838 G L A R - - - - D S N Y V
Deletion of HSDN845-848P (SEQ ID NOs: 7 and 8)	2906 GGCCTGGCCAGAGACATCATGC---------**C**CTATGTG 838 G L A R D I M **P** Y V
PDGFRA Wild type	2060 GAAATTCGCTGGAGGGTCATTGAATCA 556 E I R W R V I E S
PDGFRA Insertion ER561-562 (SEQ ID NOs: 9 and 10)	2060 GAAATTCGCTGGAGG**GAGAGG**GTCATTGAATCA 556 E I R W R **E R** V I E S
PDGFRA Wild type	2081 GAATCAATCAGCCCGGATGGACATGAATATATT 563 E S I S P D G H E Y I
PDGFRA Deletion SPDGHE566-571R (SEQ ID NOs: 11 and 12)	2081 GAATCAATC----------**CCG**TATATT 563 E S I - - - - - **R** Y I
PDGFRA Wild type (SEQ ID NOs: 1 and 2)	2906* GGCCTGGCCAGAGACATCATGCATGATTCGAACTATGTG 838 G L A R D I M H D S N Y V
PDGFRA Deletion RD841-842KI (SEQ ID NOs: 24 and 25)	2906 GGCCTGGCCA**AAAT**CATCATGCATGATTCGAACTATGTG 838 G L A **K I** I M H D S N Y V
PDGFRA Wild type	2060 GAAATTCGCTGGAGGGTCATTGAATCAATCAGCCCGGAT 556 E I R W R V I E S I S P D
V561D (SEQ ID NOs: 20 and 21)	2060 GAAATTCGCTGGAGGG**A**CATTGAATCAATCAGCCCGGAT 556 E I R W R **D** I E S I S P D
PDGFRA Deletion RVIES560-564 (SEQ ID NOs: 22 and 23)	2060 GAAATTCGCTGG----------ATCAGCCCGGAT 556 E I R W - - - - - I S P D

*Numbering as in SEQ ID NO: 1 and SEQ ID NO: 2.

Claim 66 is objected to for use of the acronym "GIST". Though this is an art-recognized acronym, Applicants have done as suggested and spelled out the term the first time it is used in the claims.

Claims 69 and 72 are objected to for inconsistencies in hyphenation between these claims and the parent claims from which they depend. Applicants thank the Examiner for noting this inconsistency. Both claims are amended to be consistent with other uses of the specific terms objected to.

Claim 74 is objected to because the word "or" was omitted from between parts (a) and (b). By this amendment, the missing "or" has been inserted. Applicants thank the Examiner for noting this clerical error.

In view of the above comments and amendments, Applicants respectfully request withdrawal of all of the objections to the claims.

Freedom from Prior Art

Applicants note that no rejections were raised under §102 or §103, and that no prior art references were cited in the pending Office action. Applicants understand that the claims, at least so far as they were examined for the pending Office action, have therefore been deemed free of the prior art.

Claim Rejections -- §112, 1st paragraph, enablement

Claims 63-78 are rejected on the ground that the specification allegedly does not enable the full breadth of these claims. In particular, it is alleged that Applicants' specification does not reasonably provide enablement for methods of detecting "a biological condition associated with an activating PDGFRA mutation in a subject" across all of the activating mutations comprising "a variant nucleic acid sequence shown in one or more of positions 2072 through 2107 or [2916] through 2937 of SEQ ID NO: 26." Thus, it appears that the allegation of failed enablement addresses two aspects of Applicants' claims – the biological condition(s) being detected, and the potential variants in PDGFRA. Applicants traverse both aspects of this rejection, to the extent it might be maintained against the amended claims submitted herewith.

Variants in PDGFRA

Applicants first note that claim 63 has been amended herewith to correct a clerical error (substitution of "2090" for "2916"), as discussed elsewhere herein. This amendment is believed to address the over breadth concern discussed in the second paragraph of page 6 of the pending action, which refers to "a total of 847 residues that can potentially be mutated". Thus, the scope of mutations encompassed by the pending claims now does not differ significantly from that described in reference to the consensus sequence in SEQ ID NO: 26. In view of this amendment, and as indicated clearly in the sequence listing and specification, the regions of variation are 2072-2107 and 2916-2937 – that is, 35 + 21 = 56 residues that can potentially be mutated (or missing). This is not an unreasonable breadth of variation, given the overall length of PDGFRA

(1089 amino acids) coupled with the description in the specification – even if all of the possible 56 residues were mutated from the reference wildtype sequence, **this is less than 5% variation** .

Biological Conditions

For the sake of expeditious prosecution, Applicants herewith amend claim 63 such that the method pursued in the current claims is a method of "detecting a neoplasia associated with an activating platelet derived growth factor receptor alpha (PDGFRA) mutation in a subject". Rights in any scope removed from consideration by this amendment are expressly reserved, and Applicants by this amendment are not admitting that the specification is not enabled for biological conditions other than neoplasias. Further, Applicants assert that the specification is enabling for the claimed methods of detecting a neoplasia associated with an activating PDGFRA mutation in a subject.

As acknowledged in the Office action, Applicants' specification focuses on gastrointestinal stromal tumors (GISTs). Applicants state in the specification (page 28, line 10) that, "These [novel PDGFRA activating] mutations were initially discovered in GISTs." Based on this, Applicant in the next sentence of the specification predicted "It is expected that other human cancers will have identical or similar mutations…" to those disclosed in the application (page 28, lines 10-11). As noted in the Office action, Applicants also predict in Example 2 of the specification that "additional mutations will be identified at least in positions similar to those identified herein."

Since the filing of Applicants' application, these fully enabled predictions have been borne out, and PDGFRA mutations of the type described by Applicants in GIST have been reported in other neoplasias. Such mutations have been indentified in non-small cell lung cancer (del SPDGHE566-571K - which is variant of one mutation described in Applicants' subject application) (Thomas *et al.* "High-throughput oncogene mutation profiling in human cancer." *Nat. Genet.* 39:347-351, 2007). The Cell Signaling Technology group has reported the frequent finding of PDGFRA activation in non-small cell lung cancer (Rikova *et al.* "Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer." *Cell* 131:1190-1203, 2007). In addition, several other human tumors have been found in association with PDGFRA

kinase mutations including familial intestinal neurofibromatosis (which might be KIT-negative tumors with germline Y555C PDGFRA gain-of-function mutations) (de Raedt *et al.* "Intestinal neurofibromatosis is a subtype of familial GIST and results from a dominant activating mutation in PDGFRA." *Gastroenterology* 131:1907-1912, 2006), and intestinal fibrous polyps (Pasini *et al.* "Multiple gastrointestinal stromal tumors caused by platelet-derived growth factor receptor α gene mutations: a case associated with a germline V561D defect." *J. Clin. Endocrinol. Metab*, 2007), and intestinal lipomas (*Id.*). Additional PDGFRA mutations (such as a frameshift deletion in exon 23) have been seen in brain tumors (Rand *et al.* "Sequence survey of receptor tyrosine kinases reveals mutations in glioblastomas." *Proc. Natl. Acad. Sci. U.S.A* 102:14344-14349, 2005). Exon 10 PDGFRA mutations have been reported in Merkel cell carcinoma (Swick *et al.*, "Platelet-derived growth factor receptor alpha mutational status and immunohistochemical expression in Merkel cell carcinoma: implications for treatment with imatinib mesylate." *J. Cutan. Pathol.* 35:197-202, 2008). Very recently, a group in Germany has identified typical GIST-type PDGFRA mutations (that is, typical to the mutations identified by Applicants' in the subject application) in benign polyps of the GI tract that are called "inflammatory fibroid polyps" (Schildhaus *et al.* "Inflammatory fibroid polyps harbour mutations in the platelet-derived growth factor receptor alpha (PDGFRA) gene." *J. Pathol.* 216:176-182, 2008). Copies of each of the references cited in the above paragraph are provided herewith, as **Exhibits A-G**. In view of these representative teachings, Applicants assert that their specification is clearly enabling for more than just identification of activating mutations in GISTs – and instead is enabling across the breadth of neoplasias more generally.

Applicants note that the claims do not require that every possible neoplasia in fact have an activating mutation in PDGFRA. Rather, the pending claims and the specification provide a method for examining any subject to determine if they have a neoplasia associated with an activating PDGFRA mutation. Undoubtedly, there are subjects that have a neoplasia that do not have an activating PDGFRA mutation. However, Applicants are not aware of any instance of a sample from a subject that shows an activating PDGFRA mutation (and particularly, with an activating mutation that "comprises a variant nucleic acid sequence shown in one or more of positions 2072 through 2107 or 2916 through 2937 of SEQ ID NO: 26" as is currently required by claim 63) where the subject does not in fact have some type of neoplasia. There is no undue

experimentation in simply testing patient samples for the presence of a mutation, now that Applicants have indentified that activating mutations in PDGFRA are indicative of neoplasia.

The test for enablement does not hinge on predictability, but rather on whether or not the specification teaches one of skill in the art how to make and use the invention without undue experimentation. *In re Wands,* 858 F.2d 731, 737 (Fed.Cir.1988); *Genentech, Inc. v. Novo Nordisk,* 108 F.3d 1361, 1365 (Fed.Cir.1997). Lack of enablement arises where the specification requires one of ordinary skill in the art to perform "undue experimentation" to practice the invention as broadly as it is claimed. *In re Wands*, 858 F.2d at 737. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.* In fact, a considerable amount of experimentation is permissible, if it is merely routine or if the specification provides a reasonable amount of guidance in which direction the experimentation should proceed. *Id.* citing *In re Angstadt*, 537 F.2d 489, 502-504 (CCPA 1976).

The Federal Circuit identified "*Wands* factors" that may be used to determine if the amount of experimentation required to make and use an invention is unreasonable or undue. *Id.* at 737. Although not all the factors need to be considered, an enablement analysis cannot be limited to only one of these factors while ignoring others. MPEP §2164.01(a) citing *In re Wands*, 858 F.2d at 737.

Application of the Wands factors to the instant case supports a conclusion that the claims are enabled. The following Wands analysis is presented, further in rebuttal to the enablement rejection of claims 63-78:

Wands factor (1), "the quantity of experimentation necessary" to obtain members of the genus. The specification clearly teaches how to detect mutation(s) in PDGFRA in a subject in order to detect *any* neoplasia without undue experimentation. This is acknowledged in the Office action (page 7), where it is stated that "Examples 4-9 describe techniques and methods for detecting mutant PDGFRA nucleic acids and proteins in samples. Example 10 describes 'Differentiation of Individuals Homozygous versus Heterozygous for Activating Mutation(s)'…"

In addition, Example 1 describes the identification and characterization of PDGFRA mutations in subjects, using GIST as an example system. Thus, the specification provides sufficient guidance on how to detect mutations in PDGFRA in a subject, without undue experimentation.

Expanding the claimed genus from GISTs alone to any and all neoplasias is simply a matter of testing samples from subjects – the type of neoplasia does not matter. Looking at different subjects and different samples is a matter of routine experimentation at most. The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation is not undue. *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988). A considerable amount of experimentation is permissible, if it is **merely routine**, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.* Applicants submit that any experimentation would be routine and the present application provides the guidance necessary to employ the methods encompassed by the claims.

Further, Applicants note that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (*Int'l Trade Comm'n* 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). It is well known that cancer researchers typically engage in extensive experimentation. Such experimentation is not undue and therefore, cannot be the basis of a rejection under the enablement requirement of 35 U.S.C. § 112, first paragraph.

As detailed above, Applicants submit that very little experimentation is required to practice the full scope of the current claims particularly given the amount of guidance provided by the specification.

Wands factor (2), "the amount of direction or guidance presented." As discussed above and acknowledged by the Office, there is a considerable amount of direction and guidance provided by the specification. The specification describes in detail representative methods (*e.g.*,

in Examples 1 and 4-9) that can be used to detect mutant PDGFRA nucleic acids and proteins in samples. Considering the level of detail in the specification and the guidance presented, it is well within the skill of one of ordinary skill in the art to detect activating mutations in PDGFRA based on Applicants' teachings – particularly where the activating mutation comprises a variant nucleic acid sequence shown in one or more of positions 2072 through 2107 or 2916 through 2937 of SEQ ID NO: 26.

Wands factor (3), "the presence or absence of working examples." The specification includes examples showing the identification and characterization of several PDGFRA mutations in GISTS, which provide significant guidance to one of skill in the art. These include Example 1 and Example 17, as acknowledged by the Office at page 6 of the Office action.

Wands factors (4) "the nature of the invention" and (5) "the state of the prior art." The nature of the invention is detecting activating mutation(s) in PDGFRA in a subject, and particularly where the activating mutation comprises a variant nucleic acid sequence shown in one or more of positions 2072 through 2107 or 2916 through 2937 of SEQ ID NO: 26.

Applicants submit that the prior art provides a wide breadth of knowledge regarding methods of detecting mutations in nucleic acids and protein. For example, methods for performing DNA sequencing, Northern blot, Southern blot, Western blot, PCR, RT-PCR, restriction mapping and reporter gene assays were well known in the art as of the priority date of the instant application (see, for example, U.S. Patent Nos. 5,171,534; 5,487,970; 5,496,731; 4,683,202; 5,677,125; 4,675,283; 5,571,688; and 5,196,524). The specification also describes detection methods and/or identifies references that teach: use of gene probes and markers to identify mutations in subject (Example 4); methods of detecting single nucleotide alterations (Example 5); detecting nucleic acid levels (Example 6); detecting expression, level, or modification of polypeptides (Examples 7, 8 and 9); as well as differentiation of individuals homozygous versus heterozygous for activating mutations (Example 10).

Furthermore, the specification in Example 3 expressly teaches methods (including citations to prior art references) of performing clinical diagnostic tests for the presence or

absence of a mutation in a PDGFRA sequence of an individual. That Example specifically states:

> "The allele of the single base-pair mutation is determined by conventional methods including manual and automated fluorescent DNA sequencing, primer extension methods (Nikiforov, *et al.*, *Nucl Acids Res.* 22:4167-4175, 1994), oligonucleotide ligation assay (OLA) (Nickerson *et al.*, *Proc. Natl. Acad. Sci. USA* 87:8923-8927, 1990), allele-specific PCR methods (Rust *et al.*, *Nucl. Acids Res.* 6:3623-3629, 1993), RNase mismatch cleavage, single strand conformation polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), Taq-Man™, oligonucleotide hybridization, and the like. Also, see the following U.S. Patents for descriptions of methods or applications of polymorphism analysis to disease prediction and/or diagnosis: 4,666,828 (RFLP for Huntington's); 4,801,531 (prediction of atherosclerosis); 5,110,920 (HLA typing); 5,268,267 (prediction of small cell carcinoma); and 5,387,506 (prediction of dysautonomia)." (Page 24, lines 21-30)

Applicants respectfully submit that a wealth of teachings were available to skilled artisans in the prior art at the time of Applicants' filing, and the Specification as filed provides ample direction to carry out the claimed methods.

Wands factor (6), "the relative skill of those in the art." Applicants agree with the Office's assessment that the level of skill in the art is high. Those with ordinary skill in the art are individuals with advanced degrees such as a Doctoral Degree. It is expected that such practitioners would have a high level of familiarity with a broad range of technical information given the skill level of the individual. Considering that significant guidance is given in the specification for practicing the invention as claimed, and the techniques necessary are routine in the art, the specification fully enables one of ordinary skill in the art to practice the invention as claimed.

Wands factor (7), "the predictability or unpredictability of the art." As discussed above, the methods used to detect mutations in nucleic acids or proteins are standard, such that the detection of an activating mutation in PDGFRA would be well known to one of skill in the art. In addition, specific activating mutations are taught by the specification. Accordingly, Applicants submit it would be predictable, using the claimed methods, to determine if there is an activating mutation in PDGFRA in a subject.

Wands factor (8), "the breadth of the claims." The currently pending claims are directed to methods of determining whether a subject has an activating mutation in PDGFRA, where the activating mutation comprises a variant nucleic acid sequence shown in one or more of positions 2072 through 2107 or 2916 through 2937 of SEQ ID NO: 26, to detect a neoplasia in the subject. This breadth is reasonable.

Based on the teachings of the specification and the knowledge of one of skill in the art, Applicants' disclosure provides ample guidance to one of skill in the art to detect neoplasias in a subject by determining whether the subject has an activating mutation in a PDGFRA – particularly where the activating mutation comprises a variant nucleic acid sequence shown in one or more of positions 2072 through 2107 or 2916 through 2937 of SEQ ID NO: 26. For the reasons stated above, Applicants submit that claims 63-78 are fully enabled by the specification. Applicants request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Subject Matter Indicated to be Enabled

Applicants thank the Examiner for indicating, at page 4 of the pending Office action, that the specification is enabling for "a method of detecting a gastrointestinal stromal tumor (GIST) associated with an activating PDGFRA mutation in a subject, comprising determining whether the subject has an activating mutation in PDGFRA, and wherein the activating mutation comprises a variant nucleic acid shown in position 2919 of SEQ ID NO: 3." This subject matter corresponds to new claim 117 and the claims that depend therefrom (118-134). Applicants believe at least these claims are allowable, and request that this be acknowledged in the next action.

Claim Rejections -- §112, 2nd paragraph

Claims 71-74 and 78 are rejected for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention. The individual allegations of indefiniteness are addressed below.

Claim 71 is rejected as allegedly the term "the PDGFRA molecule" lacks antecedent basis. Applicants understand the rejection of claim 72 is because it depends on claim 71. Similarly, claim 73 is rejected as the term "the agent" lacks antecedent basis. Applicants understand the rejection of claim 74 is because it depends on claim 73. Applicants have amended claim 71 to correct a clerical error in its dependency – this claim now depends from claim 67 (rather than claim 63). Antecedent basis for both "the PDGFRA molecule" and "the agent" can be found in claim 67, from which all of claims 71-74 now depend. Applications believe this fully addresses the alleged indefiniteness of these claims.

Claim 78 is rejected because the phrase "wherein at least one oligonucleotide primer comprises a sequence as represented by at least 15 contiguous nucleotides shown in [specific positions in specific sequences]" is unclear. By this amendment, Applicants have clarified that the primer is "at least 15 nucleotides in length and overlapping at least one sequence variant as shown in" the enumerated positions. Applicants believe this fully addresses the alleged indefiniteness of this claim.

In view of the above comments and amendments, Applicants respectfully request withdrawal of all of the indefiniteness rejections under §112, 2nd paragraph.

Conclusion

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at the number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Tanya M. Harding/
Tanya M. Harding, Ph.D.
Registration No. 42,630